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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/424,705	06/02/2000	MELVYN LITTLE	35280047US00	8422

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EXAMINER	
ROARK, JESSICA H	

ART UNIT	PAPER NUMBER
1644	19

DATE MAILED: 03/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/424,705	Applicant(s) LITTLE ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 12-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 12-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 June 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *17* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 12/20/01 (Paper No. 18), is acknowledged.
Claims 10-11 have been cancelled previously.
Claims 12-27 have been added.
Claims 1-4 and 6-9 have been amended.
Claims 1-9 and 12-27 are pending and are under consideration in the instant application.

2. This Office Action will be in response to applicant's arguments, filed 12/20/01 (Paper No. 18). The rejections of record can be found in the previous Office Action (Paper No. 13).

It is noted that New Grounds of Rejection are set forth herein.

3. Formal drawings have been submitted which fail to comply with 37 CFR 1.84.
Please see the form PTO-948 previously provided as part of Paper No. 13.
Please note that drawing corrections are no longer being held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

*Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.*

4. The specification is again objected to for failure to comply with the requirements of 37 CFR 1.77. As set forth in MPEP 608.01(a), 37 CFR 1.77 indicates that there are certain basic requirements as to the arrangement of the specification. A general guidance as to the arrangement of the specification was previously provided in Paper No. 13. Applicant's attention is called in particular to the requirement for Section Headings as described at 37 CFR 1.77(c).

5. The objection to the language "by means of PCR" in Claim 4b is withdrawn.

6. The objection to Claims 1, 3 and 7 under 37 CFR 1.821(d) is withdrawn in view of the inclusion of the relevant numbering system (claim 1) and sequence identifiers (claims 3 and 7).

7. Claim 5 stands objected to under 37 CFR 1.821(d) for failing to recite sequence identifiers.

With respect to Applicant's comments, filed 12/20/01, that the sequences are available in non-patent literature references as cited in the specification on pages 1 and 2; the following is noted:

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

An application as filed must be complete in itself in order to comply with 35 U.S.C. 112; however this does not bar incorporation by reference. Ex parte Schwarze, 151 USPQ 426 (Bd. of Appeals, 1966). An application for a patent when filed may incorporate "essential material" by reference to (1) a United States patent or (2) an allowed U.S. application, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) support the claims, or (2) for adequate disclosure of the invention (35 U.S.C. 112). "Essential material" may not be incorporated by reference to (1) patents or applications published by foreign countries or regional patent offices, to (2) non-patent publications, to (3) a U.S. patent or application which itself incorporates "essential material" by reference or to (4) a foreign application. See In re Fouche, 169 USPQ 429; 439 F.2d 1237 (CCPA 1971).

Nonessential subject matter may be incorporated by reference to (1) patents or application published by the United states or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications or (3) non-patent publications, for purposes of indicating the background of the invention or illustrating the state of the art.

The referencing application must include (1) an abstract, (2) a brief summary of the invention, (3) an identification of the referenced patent or application, (4) at least one view in the drawing in those applications admitting of a drawing, and (5) one or more claims. Particular attention should be directed to specific portions of the referenced patent or application.

The sequences of the instantly claimed primers are deemed essential subject matter to practice the claimed invention. Thus the attempt to incorporate subject matter into this application by reference to Dubel et al. (J. Immunol. Meth. 1994; 175:89-95, IDS #2) and Gotter et al. (Tumor Targeting 1995; 1:107-114, IDS #3) is improper because these references are non-patent publications.

If Applicant relies upon these publications to support the instantly recited primers, the instant specification must be amended to provide the relevant information, including the sequences of the primers. Since these primers do not appear to be supported in the present sequence listing; Applicant is reminded that if the specification is so amended, then the added sequences must be placed in the sequence listing and a substitute CRF, Paper Copy of the Sequence Listing, and Statement that the CRF and Paper Copy are the same provided.

If the specification is amended to incorporate these sequences, Applicant is also reminded to provide a Hawkins-type declaration.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. The previous rejections under 35 U.S.C. 112, second paragraph, of claims 1-9 as set forth previously in Sections 17B, 17C, 17E, 17F and 17G of Paper No. 13 have been obviated by the amendment filed 12/2001.

10. Applicant's arguments, filed 12/20/01, have not been found convincing with respect to the use of "OKT3" as a proper noun in the instant application. However, it is noted that the specification on page 1 indicates that OKT3 is the antibody produced by the hybridoma of ATCC deposit number CRL 8001. The previous rejection under 35 U.S.C. 112, second paragraph, of claims 1-9 as set forth previously in Section 17A of Paper No. 13 is therefore withdrawn in the instant case because of the identification of the source of the antibody, which removes the ambiguity associated with trademarks.

However, Applicant is reminded that the proprietary nature of trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Although the previous rejection under 35 USC 112, 2nd paragraph has been withdrawn in the instant case because of the identification of the source of the antibody, Applicant is cautioned that the anti-CD3 monoclonal antibody marketed by Johnson & Johnson under the name ORHTOCLONE OKT®3 for acute allograft rejection is a trademark (see trademark serial numbers 73617455, 73337989 and 1204190).

It is again suggested that Applicant amend the claims to refer to "the antibody produced by the hybridoma of ATCC deposit number CRL 8001", rather than "OKT3".

11. Claims 2, 5, 8, 12-13, 15-17, 19 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 2 recites the limitations "The recombinant antibody product" and "the polar amino acid". There is insufficient antecedent basis for these limitations in the claim.

It is suggested that Applicant either amend claim 2 to depend from claim 1, or rewrite the claim to indicate "A" rather than "The", and to provide proper antecedent basis within the claim for "the polar amino acid", possibly by incorporating the language of claim 1.

B) Claim 5, 12-13, 15 and 19 recite the limitation "the primers used in step b)" (of the method of claim 4). However, amended claim 4b no longer recites any primers, therefore there is insufficient antecedent basis for this limitation in the claims.

C) Claims 8, 15-17 and 22 are indefinite in the recitation of "pHOG21" because its characteristics are not known.

Applicant's arguments, filed 12/20/01, have been fully considered but have not been found convincing for the reasons of record in Paper No. 13.

Applicant argues that pHOG21 denotes a distinct plasmid as shown in the specification and in two references from the instant inventors.

However, the use of "pHOG21" as the sole means of identifying the claimed vector renders the claims indefinite because the name is merely a laboratory designation which does not clearly define the claimed product. Different laboratories may use the same laboratory designations to define completely distinct vectors. In the absence of a full sequence or an ATCC deposit, a laboratory name and a few general features do not provide an unambiguous reference for the pHOG21 vector.

Amending the claims to recite an ATCC Accession Number would obviate this rejection.

D) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Applicant's amendment, filed 12/20/01, has obviated the previous rejection of claims 4-9 under 35 U.S.C. 112, first paragraph, scope of enablement.

14. Claims 8, 15-17 and 22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

Applicant's arguments, filed 12/20/01, have been fully considered but have not been found convincing essentially for the reasons of record in Paper No. 13.

Applicant asserts that the Examiner has not stated that the pHOG21 vector is not enabled by the disclosure of the present application. However, Applicant's attention is directed to the language of the first line of the rejection of record in Paper No. 13.

Applicant argues that the pHOG21 vector is enabled by the disclosure as filed because the specification at pages 4-5 and in Figure 1 disclose the individual components which comprise the pHOG21 vector, and because pHOG21 is also taught in Kipriyanov et al. (J. Immunol. Meth. 1996; 196:51-62, IDS #4).

However, the disclosure of the various general components of pHOG21 does not allow the skilled artisan to make exactly the same material as that contained in the instantly recited vector. The teachings of Kipriyanov et al. do not meet the requirements set forth in 37 CFR 1.801-1.809. In addition, neither the instant specification nor the cited reference provides the full nucleotide sequence of the pHOG21 vector. Thus the skilled artisan would not be able to make and use the instant invention based upon the guidance provided in the specification.

Thus the rejection is maintained as applied to the amended and newly added claims.

As previously noted, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent vector. See 37 CFR 1.801-1.809.

Alternatively, it is noted that limiting the claims to the method of claim 4 without reference to specific vectors would obviate this rejection.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. In view of Applicant's amendment, filed 12/20/01 providing evidence that Kipriyanov et al. (Protein Engineering April 1997; 10:445-453, IDS #5) was not actually dispatched until June 2, 1997; the previous rejection of claims 1-9 under 35 U.S.C. 102(b) as being anticipated by Kipriyanov et al. (Protein Engineering April 1997; 10:445-453, IDS #5) is withdrawn.

17. Claims 1-9, 12-25 and 27 are rejected under 35 U.S.C. 102(a) as being anticipated by Kipriyanov et al. (Protein Engineering April 1997 [dispatched June 2, 1997]; 10:445-453, IDS #5, see entire document).

Kipriyanov et al. teach a scFv antibody in which the cysteine at position H100A (Kabat numbering) of the OKT3 antibody has been exchanged with the polar amino acid serine (see entire document, especially page 448 "Construction and expression of anti-CD3 scFv mutants"). Kipriyanov et al. also teach by presenting the amino acid sequence in Figure 2B and also indicating that the sequence is preceded by a pelB leader sequence (page 448, 1st column, especially lines 16-18) that the antibody is a peptide that comprises the sequence of SEQ ID NO:2 (e.g., claim 23). A scFv is a single-chain antibody that is a recombinant antibody product.

Kipriyanov et al. also teach a method of producing the monoclonal scFv antibody with the C->S exchange at position H100A using the instant method steps including each limitation with respect to the primers (e.g., claim 5), pCR-Skript SK(+) vector (e.g., claim 6), SK1 primer (e.g., claim 7), pHOG21 vector (e.g., claim 8), and expression in XL1-Blue (e.g., claim 9) (see entire document, in particular the Materials and Methods on page 446 for "Cloning of the variable regions", "Construction of plasmids encoding scFv", "Construction of anti-CD3 mutants", and "E. coli expression and purification of scFv fragments").

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the prior art scFv antibody and the method of making said antibody.

Although Applicant has asserted in the amendment filed 12/20/01 that the instant claims are entitled to a priority date of May 23, 1997, the priority documents were not provided in English. Thus until a translation of said papers showing adequate written support for the instant claims has been made of record in accordance with 37 CFR 1.55, the rejection of the instant claims under 35 USC 102(a) is appropriate.

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 1-2, 4-9, 12-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kroon et al. (Pharmaceutical Res. 9:1386-1393 1992, of record) in view of Kipriyanov et al. (J. Immunol. Meth. 1996; 196:51-62, IDS #4) and in further view of Senoo et al (US Pat. No. 5,852,177, of record).

Applicant's arguments, filed 12/20/01, have been fully considered but have not been found convincing, essentially for the reasons of record in Paper No. 13.

Applicant argues that Kroon et al. describe several "candidate" amino acids that may be involved in the instability of OKT3, and that Kroon et al. do not provide evidence that the cysteine of CDR3 (i.e. position H100A) is the primary event responsible for OKT3 instability. Applicant concludes that it would not have been obvious to one of ordinary skill in the art which one amino acid would be responsible.

Applicant further argues that the ordinary artisan would not have had a reasonable expectation that an antibody in which a residue of CDR3 has been changed would retain the ability to bind its antigen because substitution of antibody CDR3, unlike the protein described by Senoo et al., would be expected to not result in a functional protein.

These arguments are addressed below in the context of a reiteration of the rejection of record as applied to the newly added claims.

The instant claims are drawn to a recombinant antibody product in which the cysteine at position H100A of the OKT3 antibody has been exchanged with the polar amino acid serine, and a method of producing this antibody.

As discussed previously, Kroon et al teach that the OKT3 antibody is inactivated while in storage as a consequence of formation of cross-links between heavy chain in the region of amino acids 99-121 (see entire document, especially page 1391-1392 bridging paragraph and the sequence of Figure 1). Although the numbering system used is different, Kroon et al. teach that the Cys in the third heavy chain CDR (i.e., CDR3) *is a likely candidate* for oxidation which would lead to degradative structural changes for OKT3 (see especially page 1390). Kroon et al. further teach using site directed mutagenesis to synthesize analogues that are more stable would be beneficial for the development of therapeutics (e.g., page 1392, last paragraph).

Although Applicant has argued that the direction to the cysteine at H100A is insufficient in Kroon et al. because other residues are also discussed; Kroon et al. clearly indicate on page 1390 that "[t]he most significant change in the peptide maps of OKT3 with long term storage was a decrease in the size of the peak corresponding to H99-121" and that "there is a non-disulfide-bonded Cys at residue 105, a likely candidate for oxidation."

Thus Kroon et al. provide clear direction to this cysteine, which is the same cysteine as that at H100A using the instant numbering system; and further teach the application of site-directed mutagenesis to generate more stable forms of OKT3. Consequently, one of ordinary skill in the art, armed with the teachings of Kroon et al. would have clearly been motivated to change this cysteine by site-directed mutagenesis.

Kroon et al. do not teach a detailed method of producing a recombinant antibody product in which the cysteine at position H100A of the OKT3 antibody has been exchanged with the polar amino acid serine, and a method of producing this antibody, nor do they produce OKT3 having the cysteine at H100A changed to a serine.

However, Kipriyanov et al. teach a method of producing scFv from hybridomas of interest by obtaining mRNA, transcribing the mRNA to cDNA, amplifying the heavy and light chain variable regions using the primers Bi5, Bi8, Bi4, and Bi3f, cloning the amplified DNA into the pCR-Skript SK(+) vector adapted for site-specific mutagenesis, insertion of the DNA into the expression vector pHOG21, and finally expression of the scFv using E. Coli XL1-Blue (see entire document, especially sections 2.2 to 2.5).

Further, Senoo et al. teach that formation of intra and interchain disulfide bonds is detrimental to protein stability (see entire document, especially column 1 to column 2, bridging paragraph) and that the conversion of a cysteine to serine to eliminates this problem and improves protein stability (e.g., column 7, lines 55-57).

Therefore it would have been obvious to one of ordinary skill in the art to apply the teachings of Kipriyanov et al. and Senoo et al. to the teachings of Kroon et al. to obtain an OKT3 antibody in which heavy chain cysteine 100A (in the instant numbering system) was replaced with serine in order to produce a more stable OKT3 antibody. Site-directed mutagenesis to produce such a molecule was well within the skill of the ordinary artisan at the time the invention was made. Primer selection and design, based upon a known sequence, would have been a matter of selection based upon the sequence to be mutated and the change introduced. Kroon et al. give clear direction to H100A, which is the Cys found in the third CDR of the heavy chain. Senoo et al. teach that mutagenesis to Ser eliminates disulfide bonding detrimental to stability. Given the teachings of the references, the ordinary artisan would have had a reasonable expectation of producing a mutated OKT3 scFv in which the Cys in CDR3 (H100A) had been exchanged for cysteine.

Applicant has argued that the ordinary artisan would not have had a reasonable expectation that an OKT3 antibody in which H100A was changed from a cysteine would still bind antigen with an appreciable binding activity.

However, it is first noted that the instant claims do not require that the antibody bind its antigen, thus Applicant is arguing limitations which are not claimed. Given the clear direction of Kroon et al. to change the cysteine residue so as to obtain an antibody with improved therapeutic potential, the ordinary artisan would have been motivated to make the change and produce the instantly recited recombinant antibody product using the instantly recited method.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection is maintained.

20. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kipriyanov et al. (Protein Engineering April 1997 [dispatched June 2, 1997]; 10:445-453, IDS #5) and Nitta et al. (The LANCET 1990; 335:368-371, IDS #9).

Kipriyanov et al. teach in Figure 2B an amino acid sequence and also indicate that the sequence is preceded by a pelB leader sequence (page 448, 1st column, especially lines 16-18). The amino acid sequence of Figure 2B preceded by a PelB leader sequence is a peptide comprising the amino acid sequence of SEQ ID NO:2. Kipriyanov et al. also teach that this peptide sequence is the OKT3 antibody variable domains in which the cysteine at position H100A has been replaced by a serine (see entire document, e.g., Abstract).

Kipriyanov et al. also teach that the substitution of cysteine with a serine resulted in greater in vitro stability compared to an OKT3 antibody in which the cysteine was present at H100A (e.g., see summary of results in Abstract).

Kipriyanov et al. do not teach a bispecific antibody comprising SEQ ID NO:2.

Nitta et al. teach a bispecific antibody comprising the anti-CD3 monoclonal antibody OKT3 and how to make it (see entire document, e.g., Abstract and "Preparation of bispecific antibody" on page 368). Nitta et al. also teach the in vitro use of the bispecific antibody comprising OKT3 in the production of LAK cells which were used in adoptive transfer experiments to successfully target glioma cells in patients and were found to be more effective than LAK cells generated without the OKT3 bispecific antibody present (see entire document, as summarized in Abstract).

Therefore, it would have been obvious to the ordinary artisan at the time the invention was made to substitute the more stable form of the OKT3 antibody taught by Kipriyanov et al. for the unmutated antibody used in the bispecific construct of Nitta et al. in order to obtain a more stable bispecific antibody for use in in vitro generation of anti-tumor LAK cells. The ordinary artisan at the time the invention was made would have been motivated to make the substitution given the teachings of Kipriyanov et al. that replacement of the H100A cysteine with serine resulted in a more stable antibody, which the ordinary artisan would have recognized as more desirable for use in the methods of Nitta et al. Given the teachings of the references, the ordinary artisan would have had a reasonable expectation of successfully producing a bispecific antibody comprising SEQ ID NO:2. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Although Applicant has asserted in the amendment filed 12/20/01 that the instant claim is entitled to a priority date of May 23, 1997, the priority documents were not provided in English. Thus until a translation of said papers showing adequate written support for the instant claims has been made of record in accordance with 37 CFR 1.55, the rejection of the instant claims under 35 USC 103(a) is appropriate.

21. No claim is allowed.

22. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
March 15, 2002

Phillip Gambel
PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
3/18/02